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13. ABSTRACT *(Maximum 200*

In 1979-80 we collected and re-examined all breast biopsies performed in Israel by a single pathologist in New York (Dr. M. Black), using his prognostic grading system, nuclear differentiation and LRE response for breast diseases. The complete cohort consisted of about 3720 women. By September 1996, 1760 benign breast disease (BBD) cases were interviewed. Preliminary data show that about 30% of the BBD women went through an additional biopsy and 11% went through ≥2, that were re-evaluated by Dr. Black. First follow-up for morbidity and mortality was done by linkage of our cohort file with that of the Cancer Registry: 2.2% with normotypic (grade 1), 3.3% of hyperplastic (grade 2), and 9% of atypic, (grade ≥3) and 4.2% of the *in-situ* Ca (grade 5) women developed BC. Median time to BC was 9.9, 9.2, 5.1, 3.1, 3-10 years respectively. Data collected from the BBD cohort women included information on hormonal and parity history, history of BBD and BC, physical activity and alcohol drinking habits. Computer programming has been concluded and frequencies of selected parameters are presented. Mortality of the invasive cancer patient's cohort was 67.2%. For 45% of the breast cancer (BC) cohort women, oncological information from medical records was abstracted.

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INTRODUCTION AND STUDY PURPOSE

Dissatisfaction with the prognostic value of a traditional pathologic categorization of BBD has led to the development of a classification of defined segments of the mammary duct system based on proliferation and the degree of atypical changes (1,2).

The essential feature of Black-Chabon grading system is based on a score of 1 to 5 describing a degree of ductal atypia. Normotypic lesions included those classifed as normoplastic (Grade 1) and hyperplastic (Grade 2). The normoplastic lesions included those conventionally categorized as cystic changes, stromal fibrosis, duct ectasia, and normal-appearing breast parenchyma. The hyperplastic lesions included those conventionally classified as intraductal papillomas, papillomatosis, adenosis, and duct hyperplasia without atypia. The term benign proliferative mastopathy was ascribed to the preceding group of conditions with duct Grades 1 to $\geq$1 to $\geq$2. Minimal, moderate and marked degrees of ductal and/or lobular atypia were graded as 3 and 4, respectively. A grading of 5 essentially coincides with the traditional category of Ca *in situ.*

The evolution of BC from normal tissue to malignancy has a long natural history which may be a multistage process that proceeds through duct cell hyperproliferation to atypia, *in situ* growth, and malignant transformation. This tumorogenesis model may be associated with several genetic, hormonal and reproductive factors that may act to depress, or enhance, the final outcome in this dynamic continuum (3).

It is recognized that a number of factors may play a role, in a stepwise manner, in the process of carcinogenesis. In this continuum, there are factors such

as oral contraceptives (OC) intake, reproductive events and breast irradiation, that can influence the risk of BC onset (4-8). Therefore, this study offers an unusual opportunity to evaluate the role of various factors in relation to baseline (start of follow-up) and final outcome in the process (end of follow-up). Such influence may be evaluated in a comparative perspective, for women with high and low baseline risks of BC (i.e. those born in Europe or America versus boen in Asia or Africa), who share an apparent common risk factor (BBD).

Our nested case-control study will allow comparing, within each pathological subgroup, the effects of several recognized factors associated with BC risk, acting before and after first BBD appearance between women who developed BC and those who did not.

The passive follow-up of the subcohort of BC will allow a better understanding of the role of demographic, pathological, and medical characteristics (including surgical and oncological treatment of BC) for further mortality (9).

The study is based on a twelve-year follow-up of the cohort of 3500 women histologically diagnosed nationwide for benign and malignant breast lesions, between July 1979 and June 1980 (10). A particular feature of the study population is that it stems from a single community but comprises subgroups with varying BC incidence; high risk women born in Europe, America and Israel, and low risk women originating from the Middle East and North Africa. The age-adjusted BC incidence rates of these groups in the late 1980's were 87.0 and 57.2 per 100,000 respectively, a gradient similar to the one observed between US whites and Africans (11).

Significance

This study offers a unique opportunity to evaluate the progression of benign and malignant breast disease on a whole community base population.

Results will contribute to shedding light in respect to the role of BBD in general, and it's specific histologic types in BC causation, taking into account interactions with main hormonal and demographic risk factors.

TECHNICAL OBJECTIVES

The specific aims are:

1. To assess morbidity patterns in a nationwide cohort of women with breast lesions by histopathological type and by ethnic origin.
2. To compare the prognostic value of Black-Chabon atypia-based grading system of BBD to the "traditional" histopathologic diagnosis, as predictors for progression from benign to malignant breast lesions.
3. To evaluate the role of selected hormonal and other factors, on the course of progression from benign to malignant breast lesions.
4. To evaluate the prognostic significance of selected specific characteristics of breast malignant neoplasms by clinical stage (TNM): histopathology; laterality of sequential neoplastic events; angiogenesis; degree of nuclear differentiation of the tumor cells (expressed as nuclear grade (NG)); and cell mediated immunity to autologous cancer cells (as manifested by microscopically demonstrable lymphoreticuloendothelial (LRE) response).
5. To assess the role of demographic and medical characteristics on the development of a second BC.
6. To establish a national datafile for subsequent long-term follow-up of this population.

WORK PROGRESS AND PRELIMINARY RESULTS

Table 1 presents the study cohort by main diagnosis, representing all women going through breast biopsy in Israel during one year period (6.1.79 - 7.1.80) and identified 12 years later. The source of the demographic information collected at time of first identification of cases consisted of the pathological records, which in many cases were found to be incomplete. Completion of demographic information was done by tracing and identifying medical records in all hospitals in Israel. Our file was then linked to the Population Registry to further update addresses and vital status (complete name and address, year of birth, father's name and place of birth) to validate identification. As can be observed, 161 cases (6.2%) were not identified. Unidentified women were found not to belong to one specific subpopulation (type of benign breast disease) but are rather distributed similarly among the various diagnostic categories, 9.7 in precancerous breast diseases and 6.3% in the normotypic benign breast disease.

Table 2 shows the interview status of the nested case control study. By 1.6.96 we completed 1769 interviews and about 300 cases are still in progress. Response was about 80%. Non response by type of diagnosis shows a similar distribution among all types of diseases.

Table 3 shows results of 12 years BC morbidity follow-up. The prognostic value of Black-Chabon grading system of benign breast diseases was confirmed in our cohort. An increased risk for breast cancer with increased grading was observed: from 2.3% in the normotypic normoplastic type of BBD (grade 1) to 8.7% in atypic precancerous mastopathy (grade 3). In the same line median time till BC diagnosis decreases with increased grading from 9.9, 9.2, 5.1 10 years. For two *in situ* cases median time till BC was 3.1 and 10.3 for the second.

Table 4 shows the standardized incidence rate and confidence interval of breast cancer among the cohort of BBD patients by Black's prognostic system pathology. There is a significant increase in the risk of breast cancer in the BBD population as compared to the expected in the general population. A significant increase in risk with increased grading (from I to III) is observed. Atypic grade ≥ 3 BBD cases have a four and a half fold greater risk of breast cancer than the expected in the general population. Analysing the effect of age and origin on SIR (Table 5) we found that the increased incidence risk persists when age (<50 and >50) and origin are taken into consideration. Tables 6-7 show the frequency of selected epidemiological hormonal factors from the analysis of data obtained from personal interviews of BBD cohort.

The frequency of subsequent BBD biopsies is presented in Table 6. Thirty percent of the study cases went through at least one additional biopsy, 11% had two or more. Fifty-nine percent of consecutive biopsies were validated by local patholgists and 33% of them by Black in N.Y..

Table 7 shows preliminary data on the associations of parity and hormonal parameters with BBD by diagnosis. Parity was higher in the more advanced grade categories. This will be explored further.

The main finding thus far is the correlation between grading and subsequent BC. Using the conventional diagnostic nomenclature (e.g. fibrocystic BBD), this pattern would have been lost and would not allow identification of women with higher risk of BC that should be followed accordingly. Findings strongly support the increased risk for BC associated with previous BBD (12-23). Further analysis of our data may provide knowledge about factors associated with the progression from BBD to BC.

Future plans

Nested case control study - Last Interviews are being completed. Double check of case identification is being done by going back to unidentified cases by a second interviewer. Genetical analysis of mutations (BRCA1-2) of familial BC and familial BBD is being considered for the next year.

Direct and inferential evidence indicates that the precursor to invasive progession is impeded by cell-mediated immunity to a particular immunogen that is characteristically expressed in the preinvasive phase of mammary carcinogenesis. Further data analysis will include evaluation of this component - Lymphocyte Reticular Endotelial (LRE) response associated with further morbidity and mortality to the tumor was made in our cohort and will also be analyzed as marker for further BC morbidity. Within grade 2 and 3 there are many cases (67%) that were designed traditionally as fibrocystic disease.

Breast cancer cohort - During the next year completion of BC follow up will be done, and a special effort is being made to identify all records on the basis of a nationwide search, in addition to hospital.

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Table 1

Breast cohort by diagnostic category and current status

Diagnostic Category (1979-80)	Total Cohort (1979-80) n	Total Cohort Identified* (1995) n
Total BBD	2615*	2454
Normotypic/ hyperplastic (Grade 1-2)	2431	2277
Atypic, precancerous (Grade 3-4)	130	126
In situ (Grade 5)	54	51
Invasive	983	840

* *For about 10% of cases no review was done by Dr. Black, the complete cohort includes these women as well, with their histopathology by local pathologist*

Table 2

Distribution of the study population by interview status

and cause of non-response

					Non-response					
Total cohort	Interviewed		In process*		Refused		Not identified		Other reasons	
	n	%	n	%	n	%	n	%	n	%
2454	1769	70.7	293	11.7	196	7.8	124	5.0	120	4.8

* *until 8.1.96*

Table 3

Development of BC in the BBD Cohort
by Black's Prognostic Grading System (1991)

Grade	Total BBD	Breast Cancer		Median time to BC (years)
		no.	%	
Normotypic-Normoplastic (Grade1)	933	21	2.3	9.9
Normotypic-Hyperplastic (Grade 2)	878	32	3.6	9.2
Atypic-Hyperplastic (Grade ≥3)	126	11	8.7	5.1
In-Situ Ca	48	2	4.2	(3.1-10.3)
Unknown	469	14	3.0	8.1
TOTAL	2454	80	3.3	8.5

Table 4

Standardized Incidence Rate (SIR)* and Confidence Interval (CI) of Breast Cancer Among Cohort of Patients With BBD by Black's Diagnostic Grading

BBD Diagnosis	Total BBD	Breast Cancer			
		Observed n	Expected n	SIR*	95% CI
Total BBD↑	2342	78	36.8	2.12	1.67-2.64
Normotypic-Normoplastic (Grade I)	893	20	13.5	1.48	0.90-2.29
Normotypic-Hyperplastic (Grade II)	842	32	13.4	2.39	1.63-3.38
Atypic-Hyperplastic (Grade III)	118	10	2.23	4.48	2.14-8.24
In-Situ Ca	47	2	1.02	1.96	0.22-7.03

* *SIR derived from cases with available demographic (age and origin) ;for 112 cases this information was missing*

↑ *see remarks to Table 1*

Table 5

Standardized Incidence Rate (SIR)
and Confidence Interval of Breast Cancer by Origin

Origin	Total BBD	Observed	Expected	SIR	95% CI
	n	n	n		
All	2342	78	36.8	2.12	1.67-2.64
Asia-Africa	676	23	8.0	2.88	1.82-4.31
Europe-America	849	33	19.0	1.74	1.20-2.44
Israel	817	22	9.8	2.24	1.41-3.40
Age			22.3	2.24	1.67-2.96
<50	181	50			
50+	526	28	14.4	1.95	1.50-2.82

see remarks to Table 1

Table 6

Frequency distribution of repeated breast biopsies among interviewed population

No. of Breast Biopsies	Total n	(%)
1*	1095	(70.1)
2	299	(19.1)
3	95	(6.1)
≥4	74	(4.7)
Total	1563↑	100

** no additional biopsy*

↑ 203 interviewed cases, one in progress

Table 7

Parity characteristics of the BBD cohort by type of Black's grading system

Parameter	TYPE OF BBD				
	Normotypic		Atypic (n=76)	*In-situ* (n=21)	Unknown Black-Chabon grading (n=288)
	Normoplastic (n=583)	Hyperplastic (n=595)			
Mean no. of pregnancies*	4.46±2.59	4.60±2.32	5.19±3.37	5.60±3.37	4.87±3.07
Mean no. of births	2.82±1.69	30±1.67	2.76±1.25	2.91±1.8	2.93±1.89
Parity:					
Nulliparous	24 (4.1)	19 (3.2)	3 (3.9)	3 (14)	21 (7.3)
Parous	359 (95.9)	576 (96.8)	73 (96.1)	17 (81)	267 (92.7)
Infertility problems:					
Yes	473 (81.1)	492 (82.7)	65 (85.5)	19 (90.5)	221 (76.7)
No	110 (18.9)	103 (17.3)	11 (14.9)	2 (9.5)	65 (22.6)
Infertility treatment:					
Yes	52 (8.9)	60 (10.1)	5 (6.6)	1 (4.8)	5 (6.6)
No	531 (91.9)	535 (89.9)	71 (93.9)	20 (95.2)	71 (93.0)
Hormonal treatment for infertility:					
Yes	160 (27.4)	156 (26.2)	14 (18.4)	4 (19)	70 (24.3)
No	423 (72.6)	439 (73.8)	62 (81.6)	17 (81)	218 (75.7)
Mean age of menstruation:	13.1±1.6	13.2±1.6	13.0±1.8	13.0±1.3	13.2±1.5
Regular menses					
Yes	46 (7.9)	56 (9.4)	14 (18.4)	5 (6.6)	22 (7.6)
No	537 (92.1)	538 (90.4)	62 (81.6)	71 (93.4)	266 (92.4)

* *p=0.04 for difference between the diagnostic categories*